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PROGRESS REPORT

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SOME PHYSIOLOGICAL EFFECTS OF SERNYL IN RODENTS

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ABSTRACT

The drug 1-(1-phenylcyclohexyl) piperidine - HCl, sernyl, was tested using forced swimming in mice and guinea pigs. In low doses sernyl shows a stimulating effect on physical performance as measured by the swim test. In higher doses sernyl depresses swimming time in both mice and guinea pigs.

INTRODUCTION

Sernyl, or 1-(1-phenylcyclohexyl)-piperidine hydrochloride, is also known as phencyclidine hydrochloride. It has been used for treating certain types of psychoneuroses (1) and as anesthetic agent (2,3) It has also been found to induce schizoid responses under certain conditions.

The fact that under some conditions the drug produced excitement and under other conditions anesthesia or tranquillization suggested that its effect on physical performance might well be investigated in selected laboratory animals.

MATERIALS AND METHODS

Albino mice (averaging 30 grams weight) and guinea pigs (averaging 700-1000 grams weight) obtained from a commercial source were used in the investigations. They were selected for uniform size but were assigned randomly to various experimental treatments. Male animals only were involved. The exact numbers used are indicated later where appropriate.

The effect of the drug on heart rate in the guinea pig was observed. Rate was monitored using a direct writing electrocardiograph.

The effect of the drug on physical performance in guinea pigs and mice was ascertained by the swim test (5,6,7). Virtually the same procedures were used as in previous reports. Sernyl was administered in various doses by injection or as an aerosol. It was dissolved in distilled water or in physiological saline. The exact pattern is given at the appropriate place later in this report.

The sernyl used was supplied by the Parke, Davis and Company to whom thanks is acknowledged at this time.

RESULTS

Sernyl in physiological saline was administered to 5 guinea pigs intraperitoneally in doses of 1.4 mg/kg given at times zero and 25 minutes respectively. A typical response is shown in figure 1. After the first dose, heart rate dropped within 10 minutes to about 65 percent of control. After the second dose, a further decrease in heart rate to about 55 percent of control was obtained. After 20 to 25 minutes longer atrio-

ventricular dissociation occurred and the experiments were terminated.

Figure 2 summarizes the effects of sernyl on swimming time in guinea pigs in batns held at 36C and 24C respectively. At the latter temperature the animals swam for a relatively brief time which decreased with increasing doses. At 36C the controls swam about 8 times longer than at 24C. Two experiments were performed at 36C. In one the sernyl was dissolved in distilled water and administered subcutaneously; in the other sernyl was dissolved in 0.9 percent sodium chloride solution and administered subcutaneously. It is clear that sernyl in physiological saline was more effective in decreasing swimming time than in distilled water.

Similar experiments performed on mice are summarized in Figure 3. In these experiments the dose response curve for sernyl in saline administered subcutaneously is parabolic. Mice were exposed to an aerosol of sernyl in such a manner that the concentration times exposure time gave a presumable inhaled dose shown on the horizontal axis in Figure 3. It is evident that with the

aersol route of administration there is a rapid, linear decrease in swimming time with increasing dose of sernyl.

The above results clearly indicate a decrease in physical performance, as measured by the swim test, in mice and guinea pigs treated with sernyl.

The lowest dose of sernyl given to mice in the above experiments was 1 mg/kg; it depressed swimming time. One experiment was performed using smaller mice than previously (20 grams average weight) and with one-tenth the previous lowest dose, e.g., 0.1 mg/kg of sernyl. Table 1 summarizes the results. At this low dose sernyl clearly improved swimming performance. Attention is called to the lower control swimming time of 8 minutes; this is explained by the 10 grams weight differential, the lower bath temperature of 24C, and by the fact that the mice in this experiment were from a different commercial source than the mice used in earlier experiments.

These experiments were repeated on the new population of mice using doses up to 4.2 micromols sernyl/kg of body weight. Between zero dose and 4.2 mols/kg swimming time varied in the following fashion:

$$y = 8 + 0.96x \qquad \text{I}$$

where y is swimming time in minutes and x is dose of sernyl in μ mols/kg. The standard error of estimate is 3 minutes. Above 5 μ mols/kg the stimulating action of sernyl is replaced by a depressing action on swimming time.

DISCUSSION

It has been claimed that injection of a non-specified dose of sernyl into rats increases oxygen consumption (8). Furthermore in vitro studies with liver homogenates and mitochondria from rats indicate that sernyl stimulates oxygen uptake by such preparations (8). The effect is observed after treatment of the preparations with 0.2 and 0.5 mM concentration of the drug. The present work suggests that low doses of sernyl in intact mice favor proved physical performance as measured by the swim test. The improved physical performance could be partially explained in terms of greater oxygen consumption.

There is clear evidence from a variety of pharmacological tests that sernyl acts principally on the central nervous system (9). The effect of sernyl may be stimulating or depressing, depending on dose. Chen and coworkers point out that hyperactivity is more prominently observed in rats and mice (9).

If the data from Figures 2 and 3 are taken and compared for mice and guinea pigs, swimming at the same temperature, with respect to effect of sernyl on performance the pattern shown in Table 2 emerges. Over the dose range considered mice show a greater depressant with respect to swimming performance effect from sernyl than do guinea pigs. On the other hand, general activity criteria suggest that mice show clear excitatory reponses to a wide variety of doses of sernyl (up to 50 mg/kg) whereas guinea pigs show signs of depression even at low doses (9).

Prediction equations were derived to relate dose of sernyl to swimming time in guinea pigs using the least squares method. The results are

for saline vehicle, $y = 154 - 56.2x$ II

for distilled water vehicle, $y = 167 - 31x$ III

Where y is swimming time in minutes and x is dose in mg/kg in each equation.

For mice the prediction equations are as follows:

aerosal route, $y = 24.38 - 4.93x$ IV

subcutaneous route, $y = 21.4 - 6.3x + 0.65x^2 - 0.02x^3$ V

Again y and x are respectively swimming time in minutes and dose in mg/kg. The results are significant at the 5 percent probability level.

An interesting comparison is available using other data obtained on guinea pigs from our laboratory. Table 3 shows the doses of various drugs required to reduce swimming time in guinea pigs by a specified percent. It is clear that sernyl is highly effective on a molar basis. It is also obvious that any stimulatory effect of sernyl in guinea pigs will be found at doses below 4.5 mols/kg. This dose range for guinea pigs is now being explored in view of the results we obtained with mice (e.g. Table 1; eq. I).

Equation V must be viewed with care. It holds true if one considers doses of sernyl only greater than 1 mg/kg. Doses between 0.1 and 1 mg/kg in mice have a stimulating effect on swimming time as explained in connection with Equation I. These results are similar to those we have found for LSD-25 (7) and hexamethonium bromide (10). Support is given by these results to the plea made by Townsend and Luckey for an organized study of the problem of hormoligosis in pharmacology (11).

It is known that sernyl decreases the capacity of mice to walk on a "rotarod" and that the decrease is proportional to the dose (9). The mice so treated show clear signs of central excitation despite the poorer physical

performance. It has been concluded that sernyl in doses of 2-4 mg/kg in mice "depresses certain structures of the central nervous system which normally control and maintain the coordination of leg muscles under various adverse conditions."(9) Whether inadequate coordination of leg muscles can account for decreased swimming performance of mice treated with sernyl is not certain. Such incoordination might serve as a partial explanation.

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TABLE I

Effect of low dose of sernyl on mean swimming time in 20 gram mice in a bath held at 24C.

Item	control, saline	0.1 mg/kg
mean, minutes ($\bar{X}$)	8	13.2
st. dev.	1.4	6.3
no. of mice (n)	5	6
ΣX	40	79.5
ΣX^2	328.5	1253.7
$(\Sigma X)^2$	1600	6320.3
$(\Sigma X)^2/n$	320	1053.4
$\Sigma(X - \bar{X})^2$	8.5	200.3
s^2	2.1	40

t equals 2.4 and with 9 degrees of freedom the differences between the means is significant at the 0.05 level..

TABLE II

Comparative effect of sernyl in mice and guinea pigs. Bath temperature 24-25C. Values are calculated as percent of control swimming times.

Dose, mg/kg	Percent Control Swimming Time	
	Mice	Guinea Pigs
0	100	100
1	54	80
2	41	75
5	24	37

TABLE III

Micromols of various drugs required to reduce swimming time in guinea pigs.

Drug	Dose, μ mols/kg	Percent Decrease
Serny1	4.5	50
Meprobamate	207	50
Meprobamate	115	33
A tetrahydrocannabinol	3.2	30
Yohimbine	9.8	50

FIGURE I

Graph showing typical effect of sernyl on guinea pig heart rate. Vertical axis, rate in beats per minute; horizontal axis, time in minutes. Arrows indicate times when 1.4 mg/kg sernyl was administered to the guinea pig.

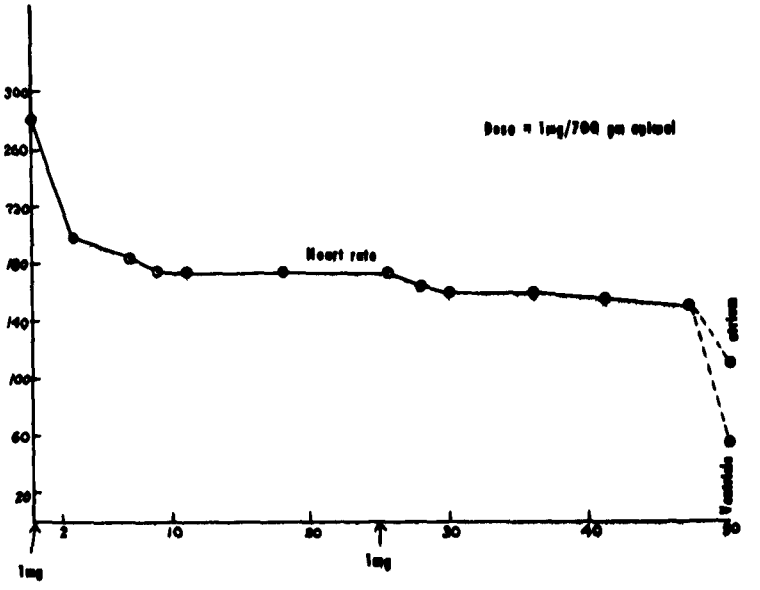

Dose = 1mg/70Q gm cyclocel
Heart rate
300
260
220
180
140
100
60
20
2
10
20
30
40
1mg
1mg

FIGURE II

Effect of sernyl administered subcutaneously in water or in physiological saline solution on guinea pigs swimming in water at two different temperatures. Horizontal axis is dose in mg/kg. Vertical bars indicate ranges. Each point is the mean of 5 animals.

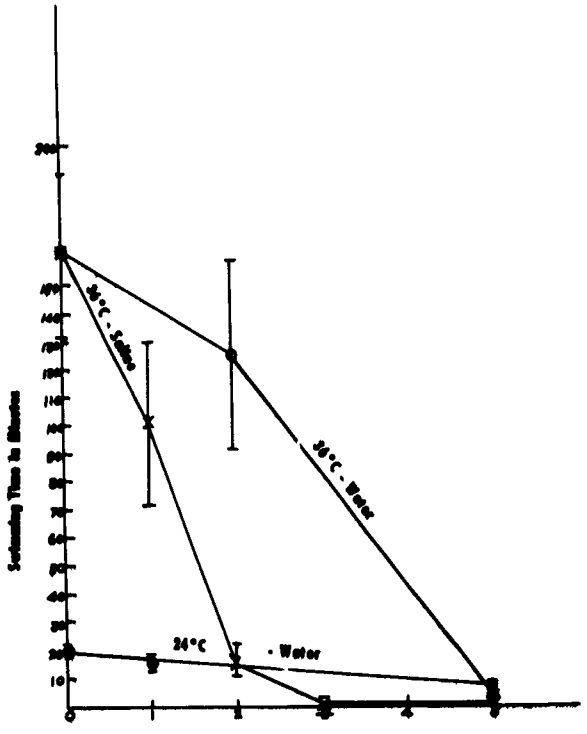
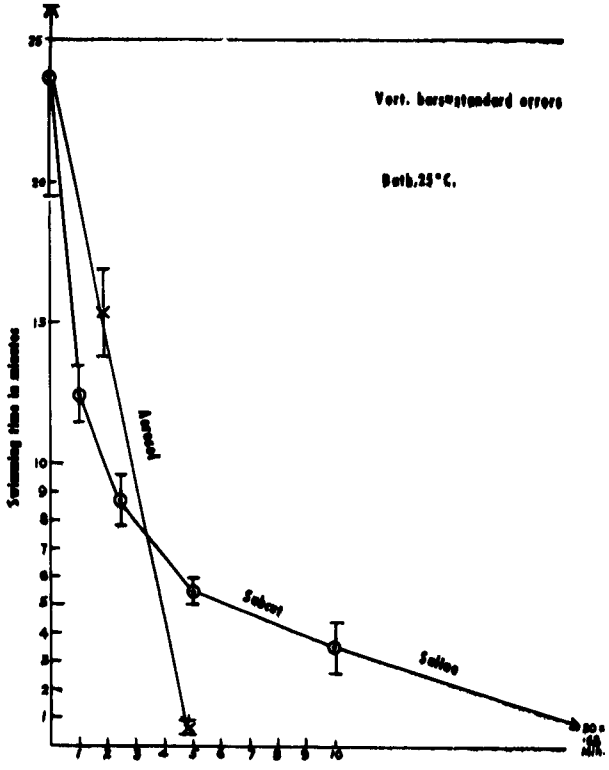

Swimming Time to Illness
24°C - Saline
24°C - Water
24°C - Water

FIGURE III

Graph showing the effect of sernyl on swimming time in mice. Each point is the mean of 5 animals. Horizontal axis, dose in mg/kg.


Vert. bars=standard errors
Bath,25°C.
Larval
Subcut
Saline
Swimming time in minutes

STATEMENT OF COMMITMENT AND POLICY

All research done in these laboratories, in connection with the present project and all other projects which involve the use of animals, was carried out in strict accord with the letter and spirit of the following principles.

GUIDING PRINCIPLES IN THE CARE AND USE OF ANIMALS

(Approved by the Council of
The American Physiological Society)

Only animals that are lawfully acquired shall be used in this laboratory, and their retention and use shall be in every case in strict compliance with state and local laws and regulations.

Animals in the laboratory must receive every consideration for their bodily comfort, they must be kindly treated, properly fed, and their surroundings kept in a sanitary condition.

Appropriate anesthetics must be used to eliminate sensibility to pain during operative procedures. Where recovery from anesthesia is necessary during the study, acceptable technic to minimize pain must be followed. Curarizing agents are not anesthetics. Where the study does not require recovery from anesthesia, the animal must be killed in a humane manner at the conclusion of the observations.

The postoperative care of animals shall be such as to minimize discomfort and pain, and in any case shall be equivalent to accepted practices in schools of Veterinary Medicine.

When animals are used by students for their education or the advancement of science such work shall be under the direct supervision of an experienced teacher or investigator. The rules for the care of such animals must be the same as for animals used for research.

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